LXXXI.—*The Constitution of Carbamides. Part III.*
The Reaction of Urea and of Thiourea with Acetic
Anhydride. Note on Potassium Thiourea.

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WHILST it is well known that acetylurea and acetylthiourea can be obtained by heating the respective parent compounds with acetic anhydride, no quantitative study of these interactions has hitherto been recorded, nor has any particular attention been given to the secondary changes which accompany the formation of the acetyl derivatives. A study of these changes has brought to light some facts of interest that support the cyclic formulæ of urea and of thiourea which have been put forward by the author (T., 1912, **101**, 2185; 1913, **103**, 1014, 2281; 1914, **105**, 924; 1915, **107**, 715).

Urea and Acetic Anhydride.

When urea is heated with acetic anhydride, carbon dioxide is freely evolved as soon as the boiling point (138°) is reached, and the greater part of the urea is decomposed with the production of acetamide and diacetamide.

The dissociation of urea and the rapid interaction of the products, ammonia and cyanic acid (in the keto-form) and acetic anhydride, are responsible for the velocity of this decomposition, which from a quantitative point of view must be considered as the primary change, and is represented by the following equations:

In consequence, the yield of acetylurea from direct acetylation is poor. Thus when urea was heated under reflux with acetic anhydride for different intervals of time, the yields of acetylurea, calculated in percentages of the theoretical, were as follows:

TABLE I.

Expt.	Time in minutes.	Acetylurea formed. Per cent.
1	2.5	21.6
" 2	5.0	34.9
" 3	10.0	34.8
" 4	15.0	27.3
" 5	20.0	23.9

Whilst the maximum yield of acetylurea was obtained after five to ten minutes' heating, the rest of the urea was found to have been completely decomposed in accordance with equations (a) and (b). The results show conclusively that direct acetylation and the main decomposition proceed simultaneously from the outset of the interaction.

These facts are in agreement with the view already put forward (T., 1913, *loc. cit.*) that when urea is heated to a temperature above its melting point in a solvent, such as acetic anhydride, dissociation of urea molecules is accompanied by a certain amount of change to the form $\text{HN:C} \begin{smallmatrix} \text{NH}_2 \\ \diagup \text{OH} \end{smallmatrix}$. It is the latter form of the molecule that is acetylated.

When the cyclic configuration of the urea molecule was changed to this form by the addition of a sufficiently strong acid, the decomposition represented by equations (a) and (b) was almost entirely suppressed, and the yield of acetylurea was largely increased.

Thus when urea was heated with acetic anhydride in presence of a small quantity of sulphuric acid, the yield of acetylurea was nearly 80 per cent. of the theoretical, and in spite of a rather violent reaction very little carbon dioxide was evolved. Acetylurea was found to separate unchanged from its solution in warm acetic anhydride, but when further heated with the reagent it was gradually decomposed with the formation of the products shown in (a) and (b); to this cause was due the fall in the yield of acetylurea after ten minutes' heating, shown in the results above.

No further acetylation of urea could be detected in these experiments. It was in an unsuccessful attempt to obtain diacetylurea in this way that Hofmann (*Ber.*, 1881, **14**, 2733) first showed that diacetamide and acetamide were produced when urea was heated with acetic anhydride.

Quite recently, Kohmann (*J. Amer. Chem. Soc.*, 1915, **37**, 2131) has shown that no diacetylurea could be obtained in this way. Now, according to the author's views, the further acetylation of acetylurea should give rise to the formation of a diacetylurea, derived from the so-called "isocarbamide" configuration, which should have the constitution $\text{HN:C} \begin{smallmatrix} \text{NH} \cdot \text{CO} \cdot \text{CH}_3 \\ \text{O} \cdot \text{CO} \cdot \text{CH}_3 \end{smallmatrix}$. Such a diacetyl derivative has been quite readily obtained by the action of acetic anhydride on acetylurea at 60° in the presence of a small quantity of sulphuric acid; the yield was quantitative, in accordance with the equation:

The compound forms slender, snow-white needles melting at 153·5°, which are sparingly soluble in cold water or alcohol.

Evidence in support of the above constitution was afforded by the fact that an acetyl group was completely removed by gently warming the compound with aqueous sodium hydroxide for a few minutes, whilst water alone at 100° hydrolysed the compound fairly rapidly, according to the equation:

Thus, in an *N*/4-solution, 21 per cent. was hydrolysed after one hour.

Acetylurea, on the other hand, is very stable in water at 100°. Diacetylurea commences to decompose at 170°; the chief products of decomposition were acetamide, acetonitrile, and carbon dioxide,

whilst small amounts of diacetamide and of cyanuric acid were also formed.

These results indicate a cleavage of the molecules in two directions, which may be represented as follows:

Considering the properties of diacetylurea, it was not surprising that it has not been found possible to prepare the compound by the direct acetylation of urea in a single operation; the heat developed in the first stage establishes a condition which precludes such a possibility.

The compound is identical with the diacetylurea (m. p. 153°) first obtained in small quantity by Schmidt (*J. pr. Chem.*, 1872, [ii], 5, 63) from the products of the interaction of carbonyl chloride and acetamide at 50°, which has been assumed, without any experimental evidence, to have the constitution $\text{CO}(\text{NH} \cdot \text{CO} \cdot \text{CH}_3)_2$.

Thiourea and Acetic Anhydride.

When thiourea was heated with acetic anhydride, the main change was direct acetylation with the production of a mixture of the monoacetyl and diacetyl derivatives; decomposition, with evolution of carbonyl sulphide, corresponding with equations (a) and (b), as in the case of urea, took place only to a very small extent, unless the heating was prolonged, when the acetyl derivatives were gradually decomposed.

As regards the production of diacetylthiourea, Kohmann (*loc. cit.*) has forestalled the author in describing the isolation of the compound for the first time.

The chief interest connected with the preparation of this compound, which, as a matter of fact, the author had isolated more than three years ago, lies in the question of its constitution and in the explanation of the conditions which promote its formation. Neither of these points was investigated by Kohmann, who has been misled in assuming that the compound must be represented by the constitutional formula, $\text{CS}(\text{NH} \cdot \text{CO} \cdot \text{CH}_3)_2$.

Like its urea analogue, this compound is derived from the "isothiurea" configuration, and has the constitution,

It has been obtained in a yield amounting to more than 75 per cent. of the theoretical by heating thiourea with acetic anhydride in the presence of hydrogen chloride. The pure compound forms bright lemon-yellow prisms, which melt at 153° (Kohmann gives $151\text{--}152^{\circ}$).

The aqueous solution was easily desulphurised in the cold on addition of an alkaline lead solution.

Diacetylthiourea was rapidly hydrolysed when heated in aqueous solution; thus, in an $N/4$ -solution at 100° , 40 per cent. was hydrolysed after thirty minutes, and 93 per cent. after one hour; as might be expected, it is much less stable in this respect than the urea analogue. Whilst the main change was the loss of the acetyl group previously in union with sulphur, in accordance with the equation:

a certain amount of the compound was decomposed in the following manner:

The latter change was more marked in the presence of a strong acid. Monoacetylthiourea was scarcely affected after heating its aqueous solution for one hour at 100° .

Advantage has been taken of the rapid hydrolysis of diacetylthiourea in order to estimate the proportion of the two acetyl derivatives produced when thiourea was heated with acetic anhydride for different intervals of time.

The following results, expressed in percentages of the theoretical yields, were obtained:

TABLE II.

CSN_2H_4 and $(\text{CH}_3\cdot\text{CO})_2\text{O}$. Ratio, 1:2 molecular proportions.
 $t = 138^{\circ}$.

	Time in minutes.	Acetyl- thiourea. Per cent.	Diacetyl- thiourea. Per cent.	Combined products. Per cent.
Expt. 6	2.5	46.9	42.3	89.2
„ 7	5.0	42.3	46.7	89.0
„ 8	10.0	37.3	50.0	87.3
„ 9	15.0	37.7	48.4	86.1

TABLE III.

CSN₂H₄ and (CH₃·CO)₂O. Ratio, 1:1·5 molecular proportions.
t = 138°.

Expt.	Time in minutes.	Acetylthiourea. Per cent.	Diacetylthiourea. Per cent.	Combined products. Per cent.
10 ...	2.5	46.6	28.5	75.1
„ 11 ...	5.0	49.5	31.1	80.6
„ 12 ...	10.0	55.9	27.4	83.3
„ 13 ...	15.0	58.6	23.7	82.3

It has not been found possible to effect a satisfactory quantitative separation of the acetyl compounds by the aid of any solvent, but in so far as the best conditions for the preparation of acetylthiourea were concerned, these have been brought to light by the results of the above experiments. Thus, when the product of Expt. 8, where the largest yield of diacetylthiourea is shown, was boiled with water for seventy minutes, a yield of pure acetylthiourea (m. p. 168°) equal to more than 82 per cent. of the theoretical, was obtained.

Before considering the information of theoretical interest supplied by the above results, it was necessary to confirm the constitution of acetylthiourea, since it has been suggested by Prätorius (*J. pr. Chem.*, 1880, [ii], **21**, 147) that this derivative should be represented by the formula $\text{HN:C} \begin{smallmatrix} \text{NH}_2 \\ \text{S} \cdot \text{CO} \cdot \text{CH}_3 \end{smallmatrix}$.

The stability of the compound, the formation of acetylcyanamide in quantitative yield on addition of ammonio-silver nitrate in the cold, and again the production of acetamide and thiocyanic acid (with its decomposition products) prove conclusively that the acetyl group is in union with nitrogen.

In further proof of the constitution of diacetylthiourea, this compound, when decomposed by heat, gave as chief products acetamide and acetyl thiocyanate,* thus:

According to the author's views, the properties of acetylthiourea may be best represented as the result of a condition of equilibrium between two molecular forms, thus:

* This compound has been shown by Dixon (T., 1905, **87**, 468) to be a mixture of thiocyanate and isothiocyanate.

the change from α to β being promoted in solution by heat, or by the presence of either an acid or a base. Diacetylthiourea would be derived from the attack of acetic anhydride on the β -form.

The almost complete absence in the early stages of the interaction of thiourea and acetic anhydride of any change corresponding with equations (a) and (b) in the case of urea is explained by the fact that thiourea is not dissociated in solution below 140° ; hence, when the proportion of acetic anhydride was favourable, both acetyl derivatives were very rapidly produced (Expts. 6 and 7, table II), and in nearly equal proportions of the theoretical.

It will be noticed that the maximum yield of diacetylthiourea was only half of the theoretical (Expt. 8); this was due to decomposition according to equation (c), the progress of which was more rapid, as the heating was prolonged, than the change of acetylthiourea to the β -form suitable for further attack by the acid anhydride. When the latter change was promoted by the addition of hydrochloric or sulphuric acid in agreement with theory, the yield of diacetylthiourea was raised to nearly 80 per cent. of the theoretical amount.

As regards the results in table III, since the proportion of acetic anhydride was not favourable for the production of diacetylthiourea, the quantities formed were naturally much lower, but they show that from the outset of the interaction a condition suitable for further acetylation must obtain, which is in agreement with the view of the constitution of acetylthiourea already stated. It may be mentioned that the highest proportion of the monoacetyl derivative formed in a single operation is shown in the results of Expt. 13.

Potassium Derivative of Thiourea.

A considerable number of additive compounds of thiourea with various metallic salts are known, but no metallic derivative of thiourea has been hitherto described.

Whilst the salts of thiourea have undoubtedly the constitution $\text{HN}:\text{C} \begin{smallmatrix} \text{NH}_2 \cdot \text{HX} \\ \text{SH} \end{smallmatrix}$, a metallic derivative would be represented by the formula $\text{HN}:\text{C} \begin{smallmatrix} \text{NH}_2 \\ \text{SM} \end{smallmatrix}$.

The compound, $\text{CSN}_2\text{H}_3\text{K}(\text{CSN}_2\text{H}_4)_2$, was easily obtained when thiourea was gently heated with potassium ethoxide or potassium hydroxide in the presence of alcohol. It crystallised from solution in felted masses of delicate needles with a satiny lustre which melted at 145° .

Attempts to obtain the compound $\text{CSN}_2\text{H}_3\text{K}$ in crystalline form free from combined thiourea have not been successful on account

of the readiness with which the potassium derivative was decomposed in solution.

On the other hand, evidence of its constitution and of the completion of the interaction, $\text{CSN}_2\text{H}_4 + \text{KOH} = \text{CSN}_2\text{H}_3\text{K} + \text{H}_2\text{O}$, was obtained by treating the residue, after heating to 120° in a current of dry hydrogen to remove all solvent, with acetic anhydride, when a large yield of diacetylthiourea was obtained.

Potassium thiourea commenced to decompose at about 160° with evolution of ammonia; the other products were potassium thiocyanate, potassium hydrosulphide, and melamine (from the polymerisation of cyanamide). These results prove that the compound has the constitution $\text{HN}:\text{C} \begin{smallmatrix} \text{NH}_2 \\ \text{SK} \end{smallmatrix}$.

EXPERIMENTAL.

The following method was adopted in estimating the amount of acetylurea formed when urea was heated with acetic anhydride alone for different intervals of time.

Six grams of urea and 15 grams of acetic anhydride were heated under reflux to the boiling point (138°), 30 c.c. of cold water were added, and the product was allowed to remain for eighteen hours. The acetylurea which separated was collected, dried at 100° , and weighed. The solubility of acetylurea in water at 15° was found to be 2.02 per cent.; hence, 0.606 gram was added in each case to the weight obtained as a correction for the amount held in solution.

The theoretical yield of acetylurea is 10.2 grams from 6 grams of urea; from the weights obtained, the results given in table I were calculated.

Preparation of Acetylurea.

A very considerable increase in the yield was obtained in the following manner: 30 grams of urea, 70 grams of acetic anhydride, and 20 grams of pure acetic acid to which 1.5 c.c. of sulphuric acid had been added were carefully heated until a fairly violent reaction started, which was checked by immersion of the flask in cold water. One hundred grams of water were added, and after a few hours the acetylurea which had separated was collected, dried, and weighed; 39.88 grams were obtained, equal to 78.2 per cent. of the theoretical. Thus, the yield was more than doubled by this modification, which is of some practical interest, since acetylurea has been used, through its bromo-derivative, in the preparation of certain "synthetic" drugs.

Preparation of Diacetylurea.

Five grams of acetylurea were heated to 60° with 10 grams of acetic anhydride and 1 c.c. of sulphuric acid was added, when almost at once the acetylurea dissolved and there was slight development of heat. On cooling, the product set to a mass of minute, slender, silky needles, which were collected and washed with ether and alcohol and proved to be pure diacetylurea. The yield, which was 7.2 grams, was quantitative. (Found, N=19.51. $C_5H_8O_3N_2$ requires N=19.44 per cent.)

Diacetylurea may be recrystallised from solution in 50 per cent. acetic acid without sensible decomposition.

Action of Heat.—The compound (7.2 grams) was heated in a short tube immersed in a glycerol-bath, which carried a thermometer and was connected with a small condenser.

The compound melted at 153.5°, at 170–180° carbon dioxide was slowly evolved, and the liquid became yellow and opalescent; at 190° a flocculent, yellow precipitate appeared, and the temperature was raised to 200° and maintained for thirty minutes. During this period, 1 gram of a colourless liquid had distilled, which proved to be acetonitrile (b. p. 82°). The residue, which had a strong odour of acetamide, was treated with water, when 0.4 gram of an orange-yellow powder separated; by concentration of the filtrate, 0.29 gram of a micro-crystalline powder was obtained, which was cyanuric acid, and amounted to 4.02 per cent. of the weight of diacetylurea taken. The crystalline residue obtained from further evaporation, after drying, weighed 2.9 grams (40.2 per cent. of the original weight taken), and was nearly pure acetamide. The orange-yellow powder would appear to be a polymerised product from acetylcyanate which had escaped decomposition, thus: $CH_3 \cdot CO \cdot OCN = CH_3 \cdot CN + CO_2$. It was insoluble in all the usual solvents, and when strongly heated charred and evolved a pungent odour; it contained nitrogen.

The foregoing results are expressed by the equations (1) and (2) already given.

Preparation of Diacetylthiourea.

Fifteen grams of thiourea were heated with 45 grams of acetic anhydride until dissolution was just complete; hydrogen chloride, from 5 grams of sodium chloride, was passed into the liquid whilst the temperature was raised to 130°. The solution, which had assumed a reddish-brown colour, was allowed to cool, and the semi-solid mass was collected, washed with ether, and dried. The yield was 25 grams, or 78.1 per cent. of the theoretical. An equally good

yield was obtained by the addition of 1 gram of sulphuric acid in place of the hydrochloric acid.

Diacetylthiourea was easily obtained in a pure state, and with very little loss, by crystallisation from its solution in 50 per cent. acetic acid, provided the temperature was not raised beyond 70°; the addition of animal charcoal readily removed the red colouring matter. (Found, S=20·4; N=17·61. $C_5H_8O_2N_2S$ requires S=20; N=17·5 per cent.)

In order to estimate the proportions of the two acetyl derivatives formed when thiourea was heated with acetic anhydride alone, the first stage in the process was carried out as in the experiments with urea. Having obtained the weight of the combined products, 1·6 grams of the well-powdered material were boiled with 40 c.c. of water under reflux for seventy minutes, after which the cold solution was titrated with *N*-sodium hydroxide (using phenolphthalein as indicator). Since 1·6 grams of pure diacetylthiourea (M.W.=160) after such treatment were found to neutralise 10 c.c. of the alkali, the percentage of diacetyl derivative present in a mixture of the two was directly obtained as a result of the titration. From this the relative proportions with reference to the theoretical yields were easily calculated (tables II and III).

The solubility of acetylthiourea in water at 15° was found to be 1·28 per cent.; hence, 0·384 gram was added in each case to the weight obtained; diacetylthiourea is very sparingly soluble in cold water.

Action of Heat on Acetylthiourea.

Ten grams were heated in a tube, immersed in a glycerol-bath, at 190—195°, when decomposition set in with brisk evolution of carbon disulphide. After the heating had been maintained for thirty minutes at this temperature, the residue was treated with water, when 0·35 gram of a pale brown, amorphous powder separated. The filtrate, on evaporation and distillation, gave 4·2 grams of acetamide, whilst theory requires 5 grams, from the equation

$$HN:C \begin{smallmatrix} \text{NH} \cdot \text{CO} \cdot \text{CH}_3 \\ \text{SH} \end{smallmatrix} = \text{CH}_3 \cdot \text{CO} \cdot \text{NH}_2 + \text{HSCN}.$$
 The carbon disulphide (1·4 grams), when shaken with water, gave a strongly acid solution, which produced on addition of ferric chloride a deep, blood-red colour due to thiocyanic acid, much of which had been decomposed, thus: $2\text{HSCN} = \text{CS}_2 + \text{CN}_2\text{H}_2$. The amorphous substance was identified as thioammeline; it gave a picrate (decomposed at 230°) identical with that obtained from a specimen of thioammeline, synthesised from the interaction of cyanamide and thiocyanic acid solution, thus:

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Nearly half a gram of dicyanodiamide was also obtained from the residue before distillation of the acetamide.

Desulphurisation of Acetylthiourea.

To 2.95 grams of acetylthiourea dissolved in 100 c.c. of water at 60°, 8.5 grams of silver nitrate in solution as the ammonio-salt were added. The filtrate, from the precipitate of silver sulphide which was immediately formed, was evaporated at 100°; from the residue acetylcyanamide in quantitative yield was obtained by extraction with ether. The silver salt was prepared by precipitation with ammonio-silver nitrate:

0.103, dissolved in dilute HNO_3 , required 5.4 c.c. $N/10\text{-KSCN}$.
 $\text{Ag} = 56.62$.

$\text{C}_3\text{H}_3\text{ON}_2\text{Ag}$ requires $\text{Ag} = 56.54$ per cent.

Acetylcyanamide was found to be quite stable at 100°.

Analyses of the Potassium Derivative of Thiourea.—The compound was instantly decomposed when dissolved in water:

0.1928 required for neutralisation 7.4 c.c. $N/10\text{-HCl}$. $\text{K} = 14.96$.

0.0596 „ 6.6 c.c. $N/10\text{-iodine}$. $\text{CH}_4\text{N}_2\text{S} = 85.26$.

$(\text{CH}_4\text{N}_2\text{S})_2\text{CH}_3\text{N}_2\text{SK}$ requires $\text{K} = 14.66$. $\text{CH}_4\text{N}_2\text{S} = 85.71$ per cent.

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